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Value of digoxin in patients with heart failure: new pieces to the puzzle

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This article refers to “Effect of digoxin in patients with heart failure and mid-range (borderline) left ventricular ejection fraction” by A.H. Abdul-Rahim *et al.*, published in this issue on pages 1139–1145.

Heart failure (HF) remains a large medical problem with an unacceptably high morbidity and mortality despite optimal medical and device treatment.¹ Digoxin is the oldest drug in cardiovascular medicine, and in the most recent HF guidelines of the European Society of Cardiology (ESC) of 2016, it received a IIb-B recommendation,¹ i.e. it may be considered in HF patients with reduced ejection fraction (HFrEF) who are in sinus rhythm, and still symptomatic despite treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) or an angiotensin-receptor neprilysin inhibitor (ARNI), a beta-blocker and a mineralocorticoid receptor antagonist (MRA), to reduce the risk of hospitalization. This IIb-B recommendation is much lower than the IA level digoxin still had in the 2001 American College of Cardiology/American Heart Association (ACC/AHA) guidelines,² and along with this change, the use of digoxin has gradually declined from more than 60% in a large European study in the 1990s³ to less than 10% in a more recent trial in patients with HF and sinus rhythm (data from COMMANDER HF⁴). The use of digoxin has also declined in patients with atrial fibrillation (AF) (and HF), and in the 2016 ESC HF guidelines, digoxin is only recommended for the treatment of patients with HFrEF and AF to slow a rapid ventricular rate.¹ Interestingly, not a single randomized clinical trial has ever been conducted in this AF population.

The recommendation for digoxin is based on one large trial (Digitalis Investigation Group, DIG), published in 1997, that was conducted in almost 8000 patients in sinus rhythm.⁵ Patients in the DIG trial were on ACE inhibitors and diuretics, but not on beta-blockers, and the use of digoxin led to a 28% reduction in hospitalizations. Since its publication, a large number of subanalyses of the DIG trial have been conducted, which demonstrated that digoxin was more effective in more advanced HF,⁶ and in patients who had lower serum digoxin levels.^{7,8}

In the present issue of the Journal, McMurray's group from Glasgow report the results of another subanalysis of the DIG trial,

i.e. the effect of digoxin in HF patients with mid-range (borderline) ejection fraction [HFmrEF, i.e. left ventricular ejection fraction (LVEF) 40–49%].⁹ In the 2016 ESC HF guidelines,¹ this group was specifically mentioned because around 20% of all HF patients fall into this category, and this population had become somewhat of a grey area.¹⁰ Indeed, in some HF studies this group had even been excluded. It appeared useful to formally identify this HF population as a separate group, because they seemed to respond differently to treatment than patients with LVEF $\geq 50\%$, and to stimulate new research into underlying pathophysiology. In the present study from Glasgow,⁹ the effect of digoxin was thus examined in HF patients with LVEF $< 40\%$ ($n = 5874$), in patients with LVEF 40–49% ($n = 1195$), and in patients with LVEF $\geq 50\%$ ($n = 719$). The primary outcome was the composite of cardiovascular death and HF hospitalization (i.e. time to first event), and in clinical terms, patients with HFmrEF resembled patients with HFrEF more than those with HF and preserved ejection fraction (HFpEF).⁹ Event rates in HFmrEF, however, were more similar to those in HFpEF than to those in HFrEF. Digoxin reduced the primary endpoint in patients with LVEF $< 40\%$ by 29% [hazard ratio (HR) 0.71, 95% confidence interval (CI) 0.65–0.77], by 17% in patients with LVEF 40–49% (HR 0.83, 95% CI 0.66–1.05), and by 12% in patients with LVEF $\geq 50\%$ (HR 0.88, 95% CI 0.65–1.19). This effect was mainly due to reduced HF hospitalizations, and this reduction was 20% in patients with LVEF 40–49% (HR 0.80, 95% CI 0.63–1.03). In other words, the effect of digoxin was in the same direction, albeit smaller in patients with HFmrEF, as it was in patients with HFrEF, while the event rate was clearly smaller and more similar to that observed in patients with HFpEF.

How can we comment on the present study and what are the potential implications?

First, digoxin was safe in HF across the whole spectrum of LVEF, i.e. also in the group of patients with HFmrEF.

Second, digoxin caused a (non-significant) 17% reduction in the primary endpoint, which was mainly due to a 20% (non-significant) reduction in HF hospitalizations. The present analysis in patients with HFmrEF was relatively small ($n = 1195$), when time-to-first event analysis is used, particularly in a long-term follow-up study

such as the DIG trial (average follow-up 37 months).¹ Indeed, in chronic diseases such as HF, which is characterized by repeat HF hospitalizations, including all hospitalizations, and not just the first, may provide a more complete picture of the effect of the drug.^{11,12} In the EMPHASIS-HF study, this increased the effect of the MRA eplerenone from a 37% (with time-to-first event analysis) to a 47% reduction (with repeat hospitalizations analysis) (both $P < 0.001$).¹¹ In the CHARM-Preserved study, the initial time-to-first event analysis showed only a borderline, not statistically significant benefit of the ARB candesartan, but with repeat hospitalizations analysis, a 25% reduction of the composite endpoint of HF hospitalizations and cardiovascular death was observed ($P = 0.003$). This was related to the fact that in the latter analysis, 939 HF hospitalizations (547 on placebo vs. 392 on candesartan) could be taken into the analysis,¹² as compared to only 509 HF hospitalizations (279 vs. 230, respectively) in the time-to-first event analysis, i.e. a large increase in power. Because of this, an increasing number of trials, such as the Affirm-AHF (NCT02937454) and PARAGON-HF study,¹³ are now using repeat hospitalizations for their primary analysis. It would be interesting to know what the effect of digoxin in the present study population of HFmrEF patients (LVEF 40–49%) would have been if the repeat hospitalizations would have been employed.

A third comment should be made about the digoxin dose. It has been well known and documented that there is a strong association between higher doses of digoxin and increased mortality,^{2,14} and this was shown not only in the DIG study,^{7,8} but also in earlier studies with digoxin,¹⁵ and was reported again recently in the ARIS-TOTLE trial.¹⁶ The general consensus is that serum digoxin concentrations ≥ 1.0 ng/mL should be avoided, and that dosing should be aimed at reaching concentrations of 0.5–0.9 ng/mL. It would be interesting to learn whether such an effect was also present in the current subanalysis in patients with HFmrEF, and indeed, it cannot be excluded that the findings could have been more favourable for digoxin if lower doses of the drug would have been used.

Clearly, some comment should be made about the limitations of the present study, and the authors have mostly acknowledged this.⁹ This relates of course to the retrospective nature of the study, its rather low power (with time-to-first event analysis), the relatively high doses of digoxin used, and—very importantly—the fact that 20–25 years ago, beta-blockers and MRAs (and ARNI) and devices were not yet used. Particularly event rates will be largely influenced by this, and of course, the effect of digoxin against a background of these drugs is largely unknown.

Despite these points, the authors are to be congratulated with the present data, since they provide a new piece to the puzzle of whether or not digoxin should have a place in the treatment of patients with HF, and if so, how, where and with which doses. Indeed, this group from Glasgow has published some provocative data on digoxin in HF before,¹⁷ and these reports are important and useful, since they help to define the role of this very cheap and potentially useful drug for these patients. Nevertheless, new controlled data in contemporary HF patients with sinus rhythm and with AF, who are treated according to current HF guidelines,¹ are very much needed.

Conflict of interest: none declared.

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